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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/644,289	05/10/1996	MOLLY F. KULESZ-MARTIN	RPP:135D-US	4031

7590 10/01/2002

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EXAMINER
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ART UNIT	PAPER NUMBER
1642	

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99

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	08/644,289	KULESZ-MARTIN, MOLLY F.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-11 and 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15* is/are allowed.

6)☒ Claim(s) *,1, 3-6,8-11 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include new ground of rejections not previously cited.

It is noted that applicant has paid for a Notice of Appeal. Applicant can either request a refund or place the funds on credit for future appeals.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 3-6, 8-11, 15-19 are being examined.

Claim 15 seems to be free of prior art and is allowable.

The following are the remaining and new grounds of rejections.

Claim Rejections - 35 USC § 112, SECOND PARAGRAPH

OK amendment

Claims 1, 3-6, 8-11, 17 and 18 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reasons already of record in paper No:19.

Applicant argues that there is clearly no ambiguity in the use of the word "active" in the claims 1, 3-6, 8-11, 15, 17, and 18, which have been rejected under 112, second paragraph.

Applicant argues that neither Harris, nor the reviewers of "Cell" journal which published the reference by Hupp et al, nor the magazine had any difficulty understanding the meaning of "active" p53 or its "function". One of skill in the art knows a myriad of effect of p53. One skill in the art already knows that p53 has a terminal negative regulatory domain that can turn off many, if not all, of the growth regulating properties of p53 under certain conditions. One of skill in the art already knows that when the negative domain is removed, the growth regulating properties of p53 can no longer be turned off. The Examiner is referred to the references cited in the information disclosure statement, and especially the reference by Hupp et al, for examples of such known information.

The arguments have been fully considered but is not found convincing for the following reasons:

The language "active" does not set forth the metes and bound of the patent protection desired, because it is not clear which activity of the wild type p53 that the claimed p53as has equivalent function with, and under which conditions wherein the wild type p53 is "active". It is well known in the art that active wild type p53 has a multitude of functional activity, such as DNA binding, DNA repair, transcriptional activation, cellular transformation, cell cycle arrest and apoptosis (programmed cell death) (Harris et al, or examples in several references cited in the information disclosure statement). Harris et al also teach that the activity of p53 is dependent on certain conditions. One of ordinary skill in the art would have expected that the function of p53as would not be exactly the same as that of wild type p53, wherein the 50 carboxy

terminal amino acids are substituted in p53as (specification p.3, first paragraph), because of the following reasons: 1) Different from p53, which is primarily found in G1 stage of cell cycle, p53as accumulates in G2 phase of cell cycle, and said difference in properties are suggestive of cellular functions distinct from p53, as admitted by Applicant (specification, p.1, 2nd paragraph, lines 14-19), 2) C-terminal basic residues have many important functions, such as influencing the secondary structure of p53, containing sites for RNA linkage or phosphorylation by casein kinase II, and being required for stable oligomer formation *in vitro* between normal and mutant p53 (Han et al, p.1981, first column, last paragraph), and 3) although the specification discloses that p53as has DNA binding activity, the actual functional activity of p53as in DNA repair, transcriptional activation, cellular transformation, cell cycle arrest and apoptosis (programmed cell death) is not disclosed in the specification, and is unpredictable, due to modification of the C-terminal basic residues. Although the specification considers making p53as, which lacks the terminal regulatory region of the C-terminus basis domain, the specification does not discloses the structure of the terminal regulatory region. It is not clear whether deletion of terminal regulatory region could effect other functions of the C-terminus basis domain, besides effecting negative regulation of p53, because it is unpredictable whether said terminal regulatory region overlaps with other regions within the C-terminus basis domain, which have many important functions.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, NEW MATTER

Claims 1, 3-6, 8-11, 17 and 18 remain rejected under 35 USC 112, first paragraph, as containing subject matter not sufficiently described in the specification, for the reasons already of record in paper No:19.

Applicant argues that the rejection of claims 1, 3-6, 8-11, 17 and 18 under 35 USC 112, first paragraph, as containing subject matter not sufficiently described in the specification, i.e. new matter, should be reversed. Applicant argues that the desirability of incorporating a unique epitope is taught in the specification. Applicant argues that in view of the discovery by the inventor of terminally modified p53 that cannot be turned off (p53as) having a terminal sequence that raises a unique antibody, the inventor concluded that p53 could be easily truncated to remove the negative regulatory domain, and a large number of different terminal sequences could be substituted that raise unique antibodies. Applicant argues that the specification on page 2, last paragraph recites synthetic p53as having terminal amino acids different from the 50 terminal amino acids of p53, and thus clearly contemplates non-p53 sequences at the terminal end. Applicant further argues that attaching a unique epitopes to proteins and peptides are routine in the art.

The arguments have been fully considered but is not found convincing for the following reasons.

The issue here is not whether one of skill in the art could attach a unique epitope to p53as. The issue here is whether contemplating of making or using a non-p53 sequence for the purpose of providing a unique epitope at anywhere within p53as is disclosed in the specification. Although the concept of substitution within the last 50

amino acids of wild type p53 is disclosed in the specification, the concept of substitution within the last 50 amino acids of wild type p53 so as to provide a unique epitope for p53sa, which is different from not only p53, but any other proteins, is not supported by the specification. In other words, contemplation of making or using non-p53 sequences at the terminal end for the purpose of providing a unique epitope for p53sa, which is different from not only p53, but any other proteins, is not supported by the specification. Furthemore, although substitution of amino acids within the last 50 amino acids of wild type p53 is supported by the specification, the location of the claimed epitope, i.e. anywhere within p53sa, is not supported by the specification.

Claim Rejections - 35 USC § 102, NEW REJECTION

Claim 16 is rejected under 35 USC 102(b) as being anticipated by Arai et al (of record).

Claim 16 is drawn to a plasmid containing a p53as gene sequence encoding a portion of the peptide of SEQ ID NO:1, which peptide will raise an antibody response.

The specification discloses that p53as is a wild type alternative spliced p53, wherein p53as is for alternative splice (p.1, lines 6-7).

It is noted that a portion could be as little as one or two amino acids. It is further noted that claim 16 encompasses a plasmid containing a p53as gene sequence of any length, provided it encodes a portion of SEQ ID NO:1.

Arai et al teach pSP65 plasmids contain clone p53-M8, having 96 bp insert of intron 10 (p.3233, first column, second paragraph and figure 4). Arai et al further teach

that the p53-M8 clone is generated by an alternative splicing of p53 (abstract and page 3235, second paragraph).

Thus plasmids containing a cDNA clone taught by Arai et al seems to be the same as the claimed plasmid, since the protein encoded by the cDNA clone taught by Arai et al certainly comprises a portion of SEQ ID NO:1, and since the plasmids taught by Arai et al is also an alternative spliced p53.

The reference does not specifically teach a plasmid containing a p53as gene sequence encoding a portion of the peptide of SEQ ID NO:1, which peptide will raise an antibody response. However, the claimed plasmid appears to be the same as the prior art plasmid. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

1. Claims 1, 3, 4 and 17 remain rejected under 35 USC 103 as being obvious over Han et al in view of Sambrook et al for the reasons already of record in paper No:19.

Applicant argues that the rejection of claims 1, 3, 4 and 17 under 35 USC 103 over Han et al in view of Sambrook et al is improper and should be reversed. Appellant

argues that the rejection is based on hindsight. Applicant argues that Han et al only interest in sequencing and thus teach against incorporating an entire p53as cDNA sequence, because it is difficult to sequence large DNA fragments. Han et al give no reason to expect, nor suggest that incorporation of a whole p53 would somehow further the study of function or be useful for such a purpose. Applicant argues that combining Han et al and Sambrook et al accomplish nothing. A generic teaching of a large amount of protein is not equivalent to saying that long sequences can or should be incorporated into plasmids. Large amount of protein and long sequences are not the same thing or even similar.

The arguments have been fully considered but is not found convincing for the following reasons: To study function of a protein, i.e. p53 and AS-p53, as suggested by Han et al, it is art standard to obtain full length protein, because it is well known in the art that fragments of a protein usually would not have biological activity. Moreover, Sambrook et al also teach that for functional studies, intact native proteins have been produced in large amount (p. 17.2, lines 10-11). Furthermore, the full length p53as protein could be readily obtained by routine techniques of cloning and expressing a plasmid containing a full length cDNA, as taught by Sambrook et al, wherein the existence of full length p53as RNA is known in the art, as taught by Han et al, and its full length cDNA could be readily obtained, *supra*. Thus the arguments that large amount of protein and long sequences are not the same thing or even similar are rendered moot, in view of the teaching of Sambrook et al that intact native proteins have been produced in large amount for functional studies.

Moreover, .In re Kerkhoven (205 USPQ 1069, CCPA 1980) summarizes:

"It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose: idea of combining them flows logically from their having been individually taught in prior art." Neither Han et al nor Sambrook et al teach a plasmid containing full length p53as. However, in the absence of unexpected results, it would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the references and to incorporate a full length cDNA p53as into a plasmid for producing full length p53as protein for the same purpose of studying function of the expressed protein. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, given the teaching of the prior art of the existence of full length p53as RNA, wherein its full length cDNA could be readily obtained, and of the importance of studying its function, in view of the teaching of the routine use of plasmid for expressing intact protein for studying its function, it would have been obvious to incorporate full length cDNA p53as into a plasmid, because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for producing large amount of intact protein for studying its function. One of ordinary skill in the art would

have expected to obtain plasmids containing full length cDNA p53as with a reasonable expectation of success.

2. Claims 5, 6, 8-11, 18 remain rejected under 35 USC 103 as being obvious over Han et al in view of Lee et al for the reasons already of record in paper No:19.

Applicant argues that the rejection of claims 5, 6, 8-11 and 18 under 35 USC 103 over Han et al in view of Lee et al is similarly flawed hindsight combination. Neither references suggests incorporating p53as into anything; therefore their combination certainly makes no such suggestion.

The arguments have been fully considered but is not found convincing for the following reasons:

To study function of a protein, i.e. p53 and AS-p53, as suggested by Han et al, it is art standard to obtain full length protein, because it is well known in the art that fragments of a protein usually would not have biological activity. Moreover, Lee et al teach the importance and advantages of using viral vectors to obtain intact, biochemically active protein in large quantities to advance investigation of the properties of that protein.

Moreover, .In re Kerkhoven (205 USPQ 1069, CCPA 1980) summarizes:

"It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose: idea of combining them flows logically from their having been individually taught in prior art.". Neither Han et al nor Lee et al teach a viral vector containing full length p53as. However, in the absence of unexpected results, it would

have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the references and to incorporate a full length cDNA p53as into a viral for producing full length p53as protein for the same purpose of studying function or properties of the expressed protein. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, given the teaching of the prior art of the existence of full length p53as RNA, wherein its full length cDNA could be readily obtained, and of the importance of studying its function, in view of the teaching of the routine use of viral vectors for expressing intact protein for studying its function or properties, it would have been obvious to incorporate full length cDNA p53as into a viral vector, because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for producing large amount of intact protein for studying its function or properties. One of ordinary skill in the art would have expected to obtain a viral vector containing full length cDNA p53as with a reasonable expectation of success.

Claim Rejections - 35 USC § 103, NEW REJECTION

Cliam 19 is rejected under 35 USC 103 (a) as being obvious over Arai et al (of record) in view of Lee et al (of record) and Sambrook et al, eds, 1987, Molecular

Cloning, A laboratory manual, 2nd ed, Cold Spring Harbor Laboratory Press, Cold spring Harbor, pages 1.3, 1.21.

Claim 19 is drawn to is drawn to a viral vector containing a p53as gene sequence encoding a portion of the peptide of SEQ ID NO:1, which peptide will raise an antibody response.

The teaching of Arai et al has been set forth above. Arai et al however does not teach a viral vector.

Lee et al teach a method for producing substantial quantities of desired polypeptides such as tumor suppressor gene products useful for study and therapeutic by expressing cDNA clones in insect cells using baculovirus vectors, since the baculovirus is eukaryotic (abstract, p.2, lines 40-45, p.4, lines 101-5, and p.5, lines 10-20). Lee et al further teach that the drawback of bacterial expression system is that bacterial cells are unable to post-translationally modify eukaryotic protein, and analysis of such proteins could be misleading if post-translational modification of proteins are required for the normal function of the protein (p.2, paragraph before last).

Sambrook et al teach that plasmids replicate in bacteria and are purified from culture of bacteria transfected with these plasmid .

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to use the baculovirus system of Lee et al as a vector for other tumor expression gene products such as the alternatively spliced p53 of Arai et al, because the viral vector system would produce large quantities of the desired polypeptides, and because the viral vectors could be used for transfection and

expression in insect cell expression system, which is superior than plasmids which are usually used in the bacterial expression system, especially if post-translational modification of proteins are required for the normal function of the protein, as taught by Lee et al, and Sambrook et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

September 27, 2002